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(54) Title: KITS AND METHODS FOR OPTIMIZING THE EFFICACY OF CHONDROPROTECTIVE COMPOSITIONS

(57) Abstract: The present invention is directed to kits which are useful for promoting one or more health benefits as defined herein. In particular, the present kits comprise: (a) a composition comprising one or more chondroprotective agents and at least about water; and (b) information selected from the group consisting of: (i) dose-form information; (ii) instruction or suggestion of ingestion of the composition within about 4 hours of ingestion of a food or beverage; and (iii) combinations thereof. The present invention is further directed to kits comprising: (a) a composition comprising one or more chondroprotective agents and at least about 80% water; and (b) a separate food or beverage. The present invention also relates to methods of enhancing a benefit associated with a composition comprising one or more chondroprotective agents and water, the method comprising administering to a mammal the composition within about 4 hours of administration of a food or beverage.

## KITS AND METHODS FOR OPTIMIZING THE EFFICACY OF CHONDROPROTECTIVE COMPOSITIONS

### FIELD OF THE INVENTION

The present invention is directed to kits which are useful for promoting one or more health benefits including, for example, joint health, bone health, cardiac health, and / or anti-inflammation. The present invention is further directed to methods of using the kits.

### BACKGROUND OF THE INVENTION

Osteoarthritis is a widespread, degenerative disease of the joints, cartilage, and other articular components. Osteoarthritis affects all ethnic groups worldwide. In addition to humans, osteoarthritis affects nearly all mammals, for example, horses and cows, as well as domestic cats and dogs. Many treatments for osteoarthritis have been proposed, all resulting in varying degrees of success.

One osteoarthritis treatment which has been recently proposed is oral administration of chondroprotective agents such as glucosamine and / or chondroitin. See e.g., Henderson, U.S. Patent No. 5,364,845, assigned to Nutramax Laboratories, issued November 15, 1994. Indeed, various commercial products are available in the marketplace, including nutritional supplements containing such agents and powders which may be formulated into beverage compositions immediately prior to use.

Typically, administration of such agents is designed to enhance proteoglycan through an increased concentration of glycosaminoglycans. Enhanced proteoglycan provides the framework for collagen and other joint components, as well as imparting flexibility, resiliency, and resistance to compression. Thus, these agents may be administered according to various methods to enhance the articular compositions or, at a minimum, inhibit the process of degradation.

The readily available compositions containing various chondroprotective agents are in dry-form, for example, in the form of tablets or capsules. These forms offer the benefit of enhancing joint or bone health, however, the forms also suffer various deficiencies. For example, these dry-forms are not convenient for use and are not beneficial for compliance to a particular regimen. Moreover, some dry-forms require formulation in water by the consumer, which introduces the elements of dosing errors and contamination. Other forms include aqueous "syrups" (e.g., highly concentrated compositions) which are also inconvenient, particularly unpalatable, and thus do not promote compliance to an effective regimen.

The present inventors have surprisingly discovered that the efficacy of the chondroprotective agent is dependent upon two factors: 1) the form of the chondroprotective composition (*i.e.*, whether in dry-form, syrup-form, or ready-to-drink form); and 2) whether the

composition is ingested at or near the time of ingestion of a food or beverage. Excitingly, the present inventors have discovered that efficacy of the chondroprotective composition is enhanced wherein the composition is ingested within about 4 hours of ingestion of a food or beverage, relative to not consuming a food or beverage during this time period. In addition to this finding, it has been surprisingly discovered that the efficacy of aqueous chondroprotective compositions is significantly greater relative to that of dry-forms and syrup-forms of chondroprotective compositions (e.g., tablets or capsules), even wherein each of these compositions is ingested within about 4 hours of ingestion of a food or beverage.

Accordingly, efficacy of chondroprotective compositions is surprisingly related to behavior of the consumer in need of treatment, in particular, the relationship between 1) ingestion of a particular form of chondroprotective composition; and 2) food or beverage intake.

Consistent with this discovery, the present inventors describe herein kits which comprise a ready-to-drink chondroprotective composition as well as information which, when followed, improves or aids efficacy of the composition. In particular, the kits comprise information which instructs or suggests ingestion of the composition within about 4 hours of ingestion of a food or beverage. Alternatively or additionally, the kits comprise information which informs the consumer that aqueous chondroprotective compositions provide enhanced efficacy relative to dry-form and / or syrup-form chondroprotective compositions having the same, or similar, chondroprotective agent. Methods of administering the present compositions within about 4 hours of administration of a food or beverage, such that an enhanced health benefit is realized, are also provided.

#### SUMMARY OF THE INVENTION

The present invention is directed to kits which are useful for promoting one or more health benefits as defined herein. In particular, the present kits comprise:

- (a) a composition comprising one or more chondroprotective agents and at least about 80% water; and
- (b) information selected from the group consisting of:
  - (i) dose-form information;
  - (ii) instruction or suggestion of ingestion of the composition within about 4 hours of ingestion of a food or beverage; and
  - (iii) combinations thereof.

Most preferably, the instruction or suggestion relates to ingestion within about 2 hours or concurrently with a food or beverage.

The present invention is further directed to kits comprising:

- (a) a composition comprising one or more chondroprotective agents and at least about 80% water; and
- (b) a separate food or beverage.

Consistent with this discovery, the present invention also relates to methods of enhancing a benefit associated with a composition comprising one or more chondroprotective agents and water, the method comprising administering to a mammal the composition within about 4 hours of administration of a food or beverage.

#### DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to kits which are useful for providing chondroprotective compositions having enhanced health benefits, and instructions or suggestions for use which encourage optimization of these benefits. Wherein this regimen is followed, compliance, and thus efficacy, is enhanced. The compositions include those which are traditional, as well as those which may be classified as "medical foods" under regulatory guidelines. Preferably, the composition is a beverage composition. The present invention is further directed to methods of using such compositions.

The compositions are suitable for mammalian use, particularly use in humans and domestic animals such as, for example, dogs, cats, horses, and cows.

Publications and patents are referred to throughout this disclosure. All references cited herein are hereby incorporated by reference.

All percentages and ratios are calculated by weight unless otherwise indicated. All percentages and ratios are calculated based on the total composition unless otherwise indicated.

All component or composition levels are in reference to the active level of that component or composition, and are exclusive of impurities, for example, residual solvents or by-products, which may be present in commercially available sources.

Referred to herein are trade names for components including various ingredients utilized in the present invention. The inventors herein do not intend to be limited by materials under a certain trade name. Equivalent materials (e.g., those obtained from a different source under a different name or catalog (reference) number) to those referenced by trade name may be substituted and utilized in the compositions, kits, and methods herein.

In the description of the invention various embodiments and / or individual features are disclosed. As will be apparent to the ordinarily skilled practitioner, all combinations of such embodiments and features are possible and can result in preferred executions of the present invention.

The compositions, kits, and methods herein may comprise, consist essentially of, or consist of any of the elements as described herein.

#### Kits of the Present Invention

The kits of the present invention are useful for providing one or more enhanced health benefits, including, for example, joint health, bone health, cardiac health, anti-inflammation and /

or efficacy benefits. Joint health benefits include, but are not limited to, preventing, inhibiting, ceasing and / or reversing the actions associated with arthritis, particularly osteoarthritis. Thus, improved joint health will provide, for example, decreased pain in the joints and / or increased flexibility. Bone health benefits include, but are not limited to, preventing, inhibiting, ceasing, and / or reversing bone loss and / or building bone mass, and / or preventing, inhibiting, ceasing, and / or reversing osteoporosis. Thus, improved bone health may provide, for example, healthy bones, stronger bones, and / or increased bone mass. Cardiac health benefits include, but are not limited to, preventing, inhibiting, ceasing, and / or reversing, for example, heart disease, atherosclerosis, and / or restenosis. Anti-inflammation benefits include, for example, preventing, inhibiting, ceasing, and / or reversing inflammation, particularly in the joints. Thus, anti-inflammation will typically result in pain reduction. Efficacy benefits are included within all of the foregoing, and include enhanced efficacy and / or bioavailability in treating, preventing, and / or ceasing joint health dysfunction, bone health dysfunction, cardiac health dysfunction, and / or inflammation.

In one embodiment of the present invention, the kits comprise:

- (a) a composition comprising one or more chondroprotective agents and at least about 80% water; and
- (b) information selected from the group consisting of:
  - (i) dose-form information;
  - (ii) instruction or suggestion of ingestion of the composition within about 4 hours of ingestion of a food or beverage; and
  - (iii) combinations thereof.

In yet another embodiment of the present invention, the kits comprise:

- (a) a composition comprising one or more chondroprotective agents and at least about 80% water; and
- (b) a separate food or beverage.

Each of these various elements of the present invention is described in considerable detail herein below. In particular, the compositions used and the information provided is described.

#### The Composition Used in the Present Kits and Methods

The present invention is directed to use of compositions which are useful in, for example, food, beverage, pharmaceutical, over-the-counter, and dietary supplement products. The products are suitable for mammalian use, particularly use in humans and domestic animals such as, for example, dogs, cats, horses, and cows. Preferably, the present compositions are directed for use in humans and domestic animals. More preferably, the present compositions are directed for use in humans, domestic dogs, and domestic cats. Most preferably, the present compositions are directed for use in humans.

The present compositions comprise one or more chondroprotective agents and water:

#### A. Chondroprotective Agent

The chondroprotective agent utilized herein may be any agent which provides joint health, bone health, and / or anti-inflammation, as described above. Many of these agents will also provide a cardiac health benefit, as also described above. Chondroprotective agents are quite well-known in the art, and the ordinarily skilled artisan has the capability to choose any such agent for use in the present invention.

Without intending to be limited by theory, the chondroprotective agent is important for enhancing joint function as the component aids in the stimulation of proteoglycan and collagen *in vivo*. Proteoglycan provides the connective tissue, for example, collagen, which is necessary for joint health. Indeed, proteoglycan is comprised of glycosaminoglycans (often termed "GAGs") which are long chains of modified sugars. Aminosugars and methylsulfonylmethane are useful for building glycosaminoglycans and proteoglycan. Additionally, the cardiac benefits of various of these components is also a beneficial feature of this component. See e.g., Morrison *et al.*, Coronary Heart Disease and the Mucopolysaccharides (Glycosaminoglycans), pp. 109 - 127 (1973).

Non-limiting examples of chondroprotective agents which are useful herein include gelatin, cartilage, aminosugars, glycosaminoglycans, methylsulfonylmethane, precursors of methylsulfonylmethane, S-adenosylmethionine, salts thereof, and mixtures thereof. Preferably, the chondroprotective agent is selected from gelatin, cartilage, aminosugars, glycosaminoglycans, S-adenosylmethionine, salts thereof, and mixtures thereof. More preferably, the chondroprotective agent is selected from aminosugars, glycosaminoglycans, S-adenosylmethionine, salts thereof, and mixtures thereof. Even more preferably, the chondroprotective agent is selected from aminosugars, glycosaminoglycans, salts thereof, and mixtures thereof. Most preferably, the chondroprotective agent is a salt of an aminosugar, particularly wherein the aminosugar is glucosamine.

Examples of these chondroprotective agents, and preferred embodiments thereof, are described in expanded detail as follows. With respect to dosing preferences, all dosage levels are based on typical human subjects (e.g., a 65 kg subject). Wherein the present composition is used in other mammals, it may be necessary to modify the dosage. Modification of dosages based on the needs of the subject is well within the skill of the ordinary artisan. It is therefore understood that these dosage ranges are by way of example only, and that daily administration can be adjusted depending on various factors. The specific dosage of the chondroprotective agent to be administered, as well as the duration of treatment are interdependent. The dosage and treatment regimen will also depend upon such factors as the specific chondroprotective agent used, the treatment indication, the efficacy of the compound, the personal attributes of the subject (such as, for example, weight, age, sex, and medical condition of the subject), and compliance with the treatment regimen.

### Gelatin

As is commonly known, gelatin is a protein obtained from the partial hydrolysis of collagen, which is the major structural and connective protein tissue in mammals. Gelatin typically contains from about 84% to about 90% protein, from about 1% to about 2% mineral salts, and from about 8% to about 15% water (these are non-limiting approximations). Gelatin typically contains specific amounts of 18 different amino acids, which are joined together to form polypeptide chains of approximately 1,000 amino acid residues per chain.

Typically, the collagen obtained for gelatin production is from animal bones and skins, e.g., from cows and pigs. Gelatin production will typically involve the subsection of collagenous material to alkaline pre-treatment, followed by hot-water extraction (providing gelatin having an iso-electric point of about 5). Acidic pre-treatment may also be utilized (providing gelatin having an iso-electric point of from about 7 to 9).

In accordance with the present invention, wherein gelatin is included within a present composition, a single dose of gelatin within the composition is preferably from about 1 mg to about 2000 mg, more preferably from about 100 mg to about 700 mg, even more preferably from about 150 mg to about 600 mg, and most preferably from about 200 mg to about 400 mg. Typically, the composition comprising the gelatin could be dosed from about once to about five times daily, preferably from about once to about three times daily, most preferably once daily.

### Cartilage

Cartilage may be chosen as the chondroprotective agent in the present compositions. As is commonly known in the art, cartilage is a tough, elastic tissue present in the joints (as well as other locations) of the bodies of various mammals. Cartilage is comprised of at least one of calcium, proteins, carbohydrate mucopolysaccharides (e.g., chondroitin), and collagen.

Particularly preferred for use herein is bovine cartilage and shark cartilage. Bovine cartilage is primarily derived from the trachea of cows (also known as bovine tracheal cartilage, or BTC). It is similar in structure to shark cartilage. Shark cartilage is a widely utilized cartilage source, as the skeletons of sharks are primarily composed of cartilage rather than bone.

In accordance with the present invention, wherein cartilage is included within a present composition, a single dose of cartilage within the composition is preferably from about 1 mg to about 2000 mg, more preferably from about 100 mg to about 700 mg, even more preferably from about 150 mg to about 600 mg, and most preferably from about 200 mg to about 400 mg. Typically, the composition comprising the cartilage is dosed from about once to about five times daily, preferably from about once to about three times daily, most preferably once daily.

### Aminosugars

One or more aminosugars may be chosen as the chondroprotective agent herein. The aminosugars are monosaccharide components (i.e., hexoses) which are modified with an amine functionality. The amine functionality may be a free amine moiety or a protected amine moiety

(e.g., N-acetyl amine). Preferably, the aminosugar is a precursor to glycosaminoglycan, which is important for construction of joint constituents (e.g., collagen). Additionally, certain aminosugars may serve to inhibit the activity of enzymes which are implicated in breakdown the cartilage in osteoarthritis (e.g., mannosamine, which has been discovered to inhibit aggrecanase). The aminosugars are well-known in the art; many aminosugars are naturally occurring.

Particularly preferred aminosugars include glucosamine, salts of glucosamine, galactosamine, salts of galactosamine, mannosamine, salts of mannosamine, as well as the N-acetyl derivatives of the foregoing, including N-acetyl glucosamine and N-acetyl galactosamine. More preferably, the aminosugars include glucosamine and salts of glucosamine, most preferably salts of glucosamine. Particularly preferred salts of glucosamine include glucosamine sulfate and glucosamine hydrochloride. The salts of glucosamine are particularly preferred to aid bioavailability to the aminosugar in addition to the bioavailability benefit achieved by the second component (as described herein below).

As an example, glucosamine provides the building block needed *in vivo* to manufacture glycosaminoglycan, which is found in cartilage. Thus, glucosamine, and other aminosugars, function not only to relieve symptoms of joint pain but also inhibits, stops, and / or reverses the degenerative process.

Typical single dosing of the aminosugars is preferably from about 1 mg to about 5000 mg, more preferably from about 100 mg to about 3600 mg, even more preferably from about 150 mg to about 2200 mg, and most preferably from about 250 mg to about 1900 mg, based on the molecular weight of glucosamine hydrochloride. For example, a particularly preferred dosage of glucosamine hydrochloride is about 1800 mg, which translates to about 1480 mg of glucosamine. All other aminosugars may be similarly dosed, based on the molecular weight of glucosamine hydrochloride. Typically, the composition comprising the aminosugar is dosed from about once to about five times daily, preferably from about once to about three times daily, most preferably once daily.

#### Glycosaminoglycans

One or more glycosaminoglycans may be utilized as the chondroprotective agent herein. The glycosaminoglycans are commonly known as GAGs, and are precursors to joint structure, for example, collagen. The glycosaminoglycans may also be important for the healing of bone.

Suitable glycosaminoglycans will be well-known to the ordinarily skilled artisan. Preferred glycosaminoglycans include chondroitin, hyaluronic acid, keratan, heparin, and dermatin, as well as salts of the foregoing. For example, chondroitin sulfate is a particularly preferred chondroitin salt. As with the aminosugars, salts of the glycosaminoglycans are particularly preferred for use herein.

As an example, chondroitin provides the structure and allows various molecules to transport through cartilage (which is important, since there is no blood supply to cartilage).



Chondroitin is a major constituent of cartilage and contains repeating chains of mucopolysaccharides.

Typical single dosing of the glycosaminoglycans is preferably from about 1 mg to about 10 grams, more preferably from about 100 mg to about 5 grams, even more preferably from about 150 mg to about 1000 mg, and most preferably from about 250 mg to about 800 mg, based on the molecular weight of chondroitin. All other glycosaminoglycans may be similarly dosed, based on the molecular weight of chondroitin. Typically, the composition comprising the glycosaminoglycan is dosed from about once to about five times daily, preferably from about once to about three times daily, most preferably once daily.

#### Methylsulfonylmethane and Precursors of Methylsulfonylmethane

The chondroprotective agent herein may also be methylsulfonylmethane, or a precursor thereof. As used herein, the term "precursor thereof" means a compound which, in mammalian systems, is converted to methylsulfonylmethane *in vivo*. Methylsulfonylmethane, and precursors thereof, are common ingredients found *in vivo* and in nature, e.g., in unprocessed foods. Without intending to be limited by theory, it is believed that the sulfur moiety present in methylsulfonylmethane, and its precursors, provides the disulfide bridging (also commonly known as "tie-bars" or "cross-links") necessary to hold the connective tissue in joints together.

While unprocessed foods contain methylsulfonylmethane, and the precursors thereof, conventional food processing and preparation causes the loss of these compounds from the foods. Therefore, commonly ingested foods may become deficient in these compounds. In these respects, methylsulfonylmethane is similar to vitamins and minerals which are typically partially or totally lost during normal food processing and preparation. It is therefore an important embodiment of this invention to include methylsulfonylmethane or a precursor thereof in the present compositions.

Non-limiting examples of precursors of methylsulfonylmethane include methionine and methyl sulfide. See e.g., Herschler et al., U.S. Patent No. 4,863,748, issued September 5, 1989. Precursors of methylsulfonylmethane are associated with a variety of health benefits, including joint benefits (such as relief from osteoarthritis and rheumatoid arthritis), as well as anti-inflammation.

In accordance with the present invention, wherein methanesulfonylmethane is included within a present composition, a single dose of methanesulfonylmethane within the composition is preferably from about 0.01 mg to about 2000 mg, more preferably from about 0.01 mg to about 500 mg, even more preferably from about 1 mg to about 200 mg, and most preferably from about 1 mg to about 100 mg. The precursors of methanesulfonylmethane may be similarly dosed, based on the molecular weights of the precursors relative to methanesulfonylmethane. Typically, the composition comprising methylsulfonyl methane, or a precursor thereof, is dosed from about

once to about five times daily, preferably from about once to about three times daily, most preferably once daily.

#### S-Adenosylmethionine

S-adenosylmethionine, which is commonly known as SAM-e, is a compound which is found in most, if not all, living cells. Without intending to be limited by theory, SAM-e is produced through reaction of the essential amino acid methionine and the energy molecule known as adenosine triphosphate (commonly known as ATP). SAM-e manufactures the components of cartilage and repairs, restores, and maintains joint function. SAM-e is made *in vivo* from the amino acid methionine, and is found in ordinary dietary sources such as meats, soybeans, eggs, seeds, and lentils.

In accordance with the present invention, wherein SAM-e is included within a present composition, a single dose of SAM-e within the composition is preferably from about 1 mg to about 2000 mg, more preferably from about 100 mg to about 700 mg, even more preferably from about 150 mg to about 600 mg, and most preferably from about 200 mg to about 400 mg. Typically, the composition comprising SAM-e is dosed from about once to about five times daily, preferably from about once to about three times daily, most preferably once daily.

#### B. Water

Water is the second necessary constituent of the present compositions. The present inventors have surprisingly discovered that bioavailability and efficacy of aqueous chondroprotective compositions is significantly greater relative to that of dry forms of chondroprotective compositions (e.g., tablets or capsules), even wherein each of these compositions is ingested within about 4 hours of ingestion of a food or beverage. Accordingly, efficacy of chondroprotective compositions is surprisingly related to behavior of the consumer in need of treatment, in particular, the relationship between 1) ingestion of a particular form of chondroprotective composition; and 2) food or beverage intake. It has therefore been found that aqueous chondroprotective compositions are surprisingly more effective relative to the corresponding dry-forms (*i.e.*, those containing less than about 2% water).

The present compositions comprise from about 80% to about 99.9999% water. Preferably, the compositions preferably comprise at least about 82% water, more preferably at least about 83% water, still more preferably at least about 84% water, even more preferably at least about 85% water, and most preferably at least about 86% water. The water included at these levels includes all added water and any water present in combination components, for example, fruit juice.

#### C. Particularly Preferred Elements of the Present Compositions

The compositions of this invention preferably exhibit a pH of from about 2 to about 7, more preferably from about 2 to about 5, still more preferably from about 3 to about 5, even more preferably from about 3.5 to about 4.5, and most preferably from about 3.7 to about 4.2.

If necessary, the present compositions may comprise one or more acidulants in order to reach, and maintain, the presently preferred pH. Composition acidity can be adjusted to and maintained within the requisite range by known and conventional methods, e.g., the use of one or more acidulants.

Organic as well as inorganic edible acids may be used to adjust the pH of the ready-to-drink beverage compositions. The acids can be present in their undissociated form or, alternatively, as their respective salts, for example, potassium or sodium hydrogen phosphate, potassium or sodium dihydrogen phosphate salts. The preferred acids are edible organic acids which include citric acid, malic acid, fumaric acid, adipic acid, phosphoric acid, gluconic acid, tartaric acid, ascorbic acid, acetic acid, phosphoric acid or mixtures thereof. The most preferred acids are citric and malic acids.

#### D. Other Optional Components of the Present Compositions

The compositions herein are typically beverage compositions, beverage concentrates, foods or supplements (including, for example, dietary supplements, over-the-counter remedies, and pharmaceutical remedies). The compositions herein may comprise additional optional components to enhance, for example, their performance in providing joint health, bone health, other health benefits, a desirable nutritional profile, and / or organoleptic properties. For example, one or more omega-3-fatty acids, bracers, flavanols, milk base solids, soluble fibers, non-caloric sweeteners, nutrients, flavoring agents, coloring agents, preservatives, emulsifiers, oils, carbonation components, and the like may be included in the compositions herein. Such optional components may be dispersed, solubilized, or otherwise mixed into the present compositions. These components may be added to the compositions herein provided they do not substantially hinder the properties of the beverage composition, particularly the provision of joint and / or bone health. Non-limiting examples of optional components suitable for use herein are given below.

##### Omega-3-Fatty Acids

In a particularly preferred embodiment of the present invention, one or more omega-3-fatty acids may be added to the present compositions. Omega-3-fatty acids are anti-inflammatory compounds which act as competitive inhibitors of the arachidonic acid cascade. The omega-3-fatty acids are precursors to the synthesis of prostaglandins which function in mammals to regulate inflammation. See e.g., Burger, U.S. Patent No. 5,843,919, issued December 1, 1998.

The omega-3-fatty acid optionally utilized herein may be any omega-3-fatty acid or combination of omega-3-fatty acids. Non-limiting examples of omega-3-fatty acids which are suitable for use herein include eicosapentaenoic acid (also known as EPA), docosahexaenoic acid (also known as DHA), and mixtures thereof.

Optionally, the omega-3-fatty acid, as well as all other oil soluble components described herein, can be added to the present compositions *via* an emulsion and / or encapsulation.

Additionally, in essentially dry compositions, the omega-3-fatty acid may be spray dried according to commonly known techniques.

Wherein one or more omega-3-fatty acids is utilized in the present compositions, the ratio of the chondroprotective agent herein and the omega-3-fatty acids is often important for optimization of health benefits, particularly joint health benefits, bone health benefits, and anti-inflammation. Preferably, the ratio of the chondroprotective agent to the total omega-3-fatty acid(s) present in the composition (on a weight to weight basis) is from about 95:5 to about 5:95, more preferably from about 75:25 to about 25:75, most preferably from about 60:40 to about 40:60. The dosage of omega-3-fatty acid(s) included in the composition is therefore preferably administered according to these guidelines. Typically dosage levels of the chondroprotective agent has been detailed herein above.

#### Bracers

As is commonly known in the art, bracers can be obtained by extraction from a natural source or can be synthetically produced. Non-limiting examples of bracers include methylxanthines, e.g., caffeine, theobromine, and theophylline. Additionally, numerous other xanthine derivatives have been isolated or synthesized, which may be utilized as a bracer in the compositions herein. See e.g., Bruns, *Biochemical Pharmacology*, Vol. 30, pp. 325 - 333 (1981) which describes, *inter alia*, xanthine, 9-methyl xanthine, 7-methyl xanthine, 3-methyl xanthine, 3,7-dimethyl xanthine, 8-chloromethyl-3,7-dimethyl xanthine, 8-hydroxymethyl-3,7-dimethyl xanthine, 3,7-diethyl xanthine, 3,7-bis-(2-hydroxyethyl) xanthine, 3-propyl-7-(dimethylaminoethyl) xanthine, 1-methyl xanthine, 1,9-dimethyl xanthine, 1-methyl-8-methylthio xanthine, 8-phenyl-1-methyl xanthine, 1,7-dimethyl xanthine, 1,7-dimethyl-8-oxo xanthine, 1,3-dimethyl xanthine, 1,3,9-trimethyl xanthine, 8-fluoro theophylline, 8-chloro theophylline, 8-bromo theophylline, 8-thio theophylline, 8-methylthio theophylline, 8-ethylthio theophylline, 8-nitro theophylline, 8-methylamino theophylline, 8-dimethylamino theophylline, 8-methyl theophylline, 8-ethyl theophylline, 8-propyl theophylline, 8-cyclopropyl theophylline, theophylline-8-propionate (ethyl ester), 8-benzyl theophylline, 8-cyclopentyl theophylline, 8-cyclohexyl theophylline, 8-(3-indolyl) theophylline, 8-phenyl theophylline, 9-methyl-8-phenyl theophylline, 8-(p-chlorophenyl) theophylline, 8-(p-bromophenyl) theophylline, 8-(p-methoxyphenyl) theophylline, 8-(p-nitrophenyl) theophylline, 8-(p-dimethylaminophenyl) theophylline, 8-(p-methylphenyl) theophylline, 8-(3,4-dichlorophenyl) theophylline, 8-(m-nitrophenyl) theophylline, 8-(o-nitrophenyl) theophylline, 8-(o-carboxyphenyl) theophylline, 8-(1-naphthyl) theophylline, 8-(2,6-dimethyl-4-hydroxyphenyl) theophylline, 7-methoxy-8-phenyl theophylline, 1,3,7-trimethyl xanthine, S-chloro caffeine, S-oxo caffeine, S-methoxy caffeine, S-methylamino caffeine, 8-diethylamino caffeine, 8-ethyl caffeine, 7-ethyl theophylline, 7-(2-chloroethyl) theophylline, 7-(2-hydroxyethyl) theophylline, 7-(carboxymethyl) theophylline, 7-(carboxymethyl) theophylline (ethyl ester), 7-(2-hydroxypropyl) theophylline, 7-(2,3-dihydroxypropyl) theophylline, 7-b-D-ribofuranosyl theophylline, 7-(glycero-

pent-2-enopyranosyl) theophylline, 7-phenyl theophylline, 7,8-diphenyl theophylline, 1-methyl-3,7-diethyl xanthine, 1-methyl-3-isobutyl xanthine, 1-ethyl-3,7-dimethyl xanthine, 1,3-diethyl xanthine, 1,3,7-triethyl xanthine, 1-ethyl-3-propyl-7-butyl-8-methyl xanthine, 1,3-dipropyl xanthine, 1,3-diallyl xanthine, 1-butyl-3,7-dimethyl xanthine, 1-hexyl-3,7-dimethyl xanthine, and 1-(5-oxohexyl)-3,7-dimethyl xanthine.

Additionally, one or more of these bracers are present in, for example, coffee, tea, kola nut, cacao pod, mate', yaupon, guarana paste, and yoco. Natural plant extracts are the preferred sources of bracers as they may contain other compounds that delay the bioavailability of the bracer thus they may provide mental refreshment and alertness without tension or nervousness.

The most preferred methylxanthine is caffeine. Caffeine may be obtained from the aforementioned plants and their waste or, alternatively, may be synthetically prepared. Preferred botanical sources of caffeine which may be utilized as a complete or partial source of caffeine include green tea, guarana, mate', black tea, cola nuts, cocoa, and coffee. As used herein, green tea, guarana, coffee, and mate' are the most preferred botanical sources of caffeine, most preferably green tea, guarana, and coffee. Mate' may have the additional benefit of an appetite suppressing effect and may be included for this purpose as well. The total amount of caffeine, in any embodiment of the present invention, includes the amount of caffeine naturally present in the tea extract, flavoring agent, botanical and any other components, as well as any added caffeine.

Any bracer utilized herein is preferably present in physiologically relevant amounts, which means that the sources used in the practice of this invention provide a safe and effective quantity to achieve the desired mental alertness.

Wherein a bracer is utilized in the present compositions, such compositions will preferably comprise from about 0.0005% to about 1%, more preferably from about 0.003% to about 0.5%, still more preferably from about 0.003% to about 0.2%, even more preferably from about 0.005% to about 0.05%, and most preferably from about 0.005% to about 0.02% of a bracer, by weight of the composition. Of course, as the skilled artisan will comprehend, the actual amount of bracer added will depend its biological effect, for example, effect of mental alertness on the consumer.

In all of the present compositions, the total amount of bracer includes any added bracer as well as any bracer naturally present in any other component of the present invention.

#### Flavanols

Flavanols are natural substances present in a variety of plants (e.g., fruits, vegetables, and flowers). The flavanols which may be utilized in the present invention can be extracted from, for example, fruit, vegetables, green tea or other natural sources by any suitable method well known to those skilled in the art. For example, extraction with ethyl acetate or chlorinated organic solvents is a common method to isolate flavanols from green tea. Flavanols may be extracted from either a single plant or mixtures of plants. Many fruits, vegetables, and flowers contain

flavanols but to a lesser degree relative to green tea. Plants containing flavanols are known to those skilled in the art. Examples of the most common flavanols which are extracted from tea plants and other members of the *Catechu gambir* (Uncaria family) include, for example, catechin, epicatechin, gallocatechin, epigallocatechin, epicatechin gallate, and epigallocatechin gallate.

The flavanols utilized in all compositions of the present invention can be in the form of a tea extract. The tea extract can be obtained from the extraction of unfermented teas, fermented teas, partially fermented teas, and mixtures thereof. Preferably, the tea extracts are obtained from the extraction of unfermented and partially fermented teas. The most preferred tea extracts are obtained from green tea. Both hot and cold extracts can be used in the present invention. Suitable methods for obtaining tea extracts are well known. See e.g., Ekanayake, U.S. Patent No. 5,879,733, issued March 9, 1999; Tsai, U.S. Patent No. 4,935,256, issued June, 1990; Lunder, U.S. 4,680,193, issued July, 1987; and Creswick, U.S. Patent No. 4,668,525, issued May 26, 1987.

The preferred source of flavanols in the compositions of the present invention is green tea. Wherein green tea, and in particular the flavanols present in green tea, are incorporated into the beverage, the present inventors have discovered that the flavanols are at least partially responsible for delaying the bioavailability of bracers, which contributes to the reduction and / or elimination of nervousness and tension typically associated with such bracers.

Alternatively, these same flavanols may be prepared by synthetic or other appropriate chemical methods and incorporated into the present compositions. Flavanols, including catechin, epicatechin, and their derivatives are commercially available.

The amount of flavanols in the compositions of the present invention can vary. However, wherein one or more flavanols are utilized, preferably from about 0.001% to about 5%, more preferably from about 0.001% to about 2%, even more preferably from about 0.01% to about 1%, and most preferably from about 0.01% to about 0.05% of one or more flavanols is utilized, by weight of the composition.

In all of the embodiments of the present invention, the total amount of flavanols includes any added flavanols as well as any flavanols naturally present in any other component of the present invention.

#### Milk Base Solids

One or more milk base solids may also optionally be included in the compositions of the present invention. As used herein, milk base means milk from one or more mammals or a plant-derived milk, and includes, for example, fermented milk, lactic acid beverages obtained by lactic acid fermentation or otherwise acidified, sterilized milk base, liquid milk, and milk products such as skim milk powder or whole milk powder or other powdered forms of milk. As used herein, milk base solids means the solids content or dry matter of milk base.

Wherein one or more milk base solids is utilized, the desired total level of milk base solids, calculated on a milk solids basis for the compositions of the present invention, is from about 0.001% to about 15%, preferably from about 0.005% to about 10%, and most preferably from about 0.1% to about 5%. The total amount of milk base solids includes any added milk base solid as well as any milk base solid naturally present in any other component of the present invention.

#### Soluble Fibers

One or more soluble fibers may also optionally be included in the compositions of the present invention to provide, for example, nutritive benefits. Soluble fibers which can be used singularly or in combination in all embodiments of the present invention include but are not limited to pectins, psyllium, guar gum, xanthan gum, alginates, gum arabic, fructo-oligosaccharides, inulin, agar, and carrageenan. Preferred among these soluble fibers are at least one of guar gum, xanthan, and carrageenan, most preferably at least one of guar gum and xanthan. These soluble fibers may also serve as stabilizing agents in the various embodiments of this invention.

Particularly preferred soluble fibers for use herein are glucose polymers, preferably those which have branched chains. Preferred among these soluble fibers is one marketed under the trade name Fibersol2, commercially available from Matsutani Chemical Industry Co., Itami City, Hyogo, Japan.

Pectin and fructo-oligosaccharides are also preferred soluble fibers herein. Even more preferably, pectin and fructo-oligosaccharides are used in combination. The preferred ratio of pectin to fructo-oligosaccharide is from about 3:1 to about 1:3, by weight of the composition. The preferred pectins have a degree of esterification higher than about 65%.

The preferred fructo-oligosaccharides are a mixture of fructo-oligosaccharides composed of a chain of fructose molecules linked to a molecule of sucrose. Most preferably, they have a nystose to kestose to fructosyl-nystose ratio of about 40:50:10, by weight of the composition. Preferred fructo-oligosaccharides may be obtained by enzymatic action of fructosyltransferase on sucrose such as those which are, for example, commercially available from Beghin-Meiji Industries, Neuilly-sur-Seine, France.

Preferred pectins are obtained by hot acidic extraction from citrus peels and may be obtained, for example, from Danisco Co., Braband, Denmark.

Wherein a soluble fiber is utilized, the desired total level of soluble dietary fiber for the compositions of the present invention is from about 0.01% to about 15%, preferably from about 0.1% to about 5%, more preferably from about 0.1% to about 3%, and most preferably from about 0.2% to about 2%, by weight of the composition. The total amount of soluble dietary fiber includes any added soluble dietary fiber as well as any soluble dietary fiber naturally present in any other component of the present invention.

#### Sweeteners

The compositions of the present invention can, and typically will, contain an effective amount of one or more sweeteners, including carbohydrate sweeteners and natural and/or artificial no/low calorie sweeteners. The amount of the sweetener used in the beverages of the present invention typically depends upon the particular sweetener used and the sweetness intensity desired. For no/low calorie sweeteners, this amount varies depending upon the sweetness intensity of the particular sweetener.

The compositions of the present invention can be sweetened with any of the carbohydrate sweeteners, preferably monosaccharides and / or disaccharides. Sweetened beverages will typically comprise from about 0.1% to about 20%, most preferably from about 6 to about 14%, sweetener. These sugars can be incorporated into the beverages in solid or liquid form but are typically, and preferably, incorporated as a syrup, most preferably as a concentrated syrup such as high fructose corn syrup. For purposes of preparing beverages of the present invention, these sugar sweeteners can be provided to some extent by other components of the beverage such as, for example, the fruit juice component and / or flavors.

Preferred sugar sweeteners for use in beverage products of the present invention are sucrose, fructose, glucose, and mixtures thereof, particularly sucrose and fructose. Fructose can be obtained or provided as liquid fructose, high fructose corn syrup, dry fructose or fructose syrup, but is preferably provided as high fructose corn syrup. High fructose corn syrup (HFCS) is commercially available as HFCS-42, HFCS-55 and HFCS-90, which comprise 42%, 55% and 90%, respectively, by weight of the sugar solids therein, as fructose. Other naturally occurring sweeteners or their purified extracts, such as glycyrrhizin, stevioside, the protein sweetener thaumatin, the juice of Luo Han Guo (containing the sweet mogrosides) disclosed in, for example, Fischer et al., U. S. Patent No. 5,433,965, issued July 18, 1995, and the like can also be used in the beverages of the present invention.

Effective levels of non-caloric sweeteners may optionally be used in the compositions of the present invention to further sweeten such compositions. Non-limiting examples of non-caloric sweeteners include aspartame, saccharine, cyclamates, acesulfame K, L-aspartyl-L-phenylalanine lower alkyl ester sweeteners, L-aspartyl-D-alanine amides such as, for example, those disclosed in Brennan et al., U.S. Patent No. 4,411,925, issued 1983, L-aspartyl-D-serine amides such as, for example, those disclosed in Brennan et al., U.S. Patent No. 4,399,163, issued 1983, L-aspartyl-hydroxymethyl alkane amide sweeteners such as, for example, those disclosed in Brand, U.S. Patent No. 4,338,346, issued 1982, L-aspartyl-1-hydroxyethylalkane amide sweeteners such as, for example, those disclosed in Rizzi, U.S. Patent No. 4,423,029, issued 1983, glycyrrhizins, and synthetic alkoxy aromatics. Aspartame and acesulfame-K are the most preferred non-caloric sweeteners utilized herein, and may be utilized alone or in combination.



Wherein one or more sweeteners are utilized herein, the total non-caloric sweetener is preferably utilized at levels from about 0.0001% to about 5%, more preferably from about 0.001% to about 3%, still more preferably from about 0.005% to about 2%, even more preferably from about 0.01% to about 1%, and most preferably from about 0.01% to about 0.05%, by weight of the composition.

#### Nutrients

The compositions herein may optionally, but preferably, be fortified further with one or more nutrients, especially one or more vitamins and / or minerals. The U.S. Recommended Daily Intake (USRDI) for vitamins and minerals are defined and set forth in the Recommended Daily Dietary Allowance-Food and Nutrition Board, National Academy of Sciences-National Research Council.

Unless otherwise specified herein, wherein a given mineral is present in the composition, the composition typically comprises at least about 1%, preferably at least about 5%, more preferably from about 10% to about 200%, even more preferably from about 40% to about 150%, and most preferably from about 60% to about 125% of the USRDI of such mineral. Unless otherwise specified herein, wherein a given mineral is present in the composition, the composition comprises at least about 1%, preferably at least about 5%, more preferably from about 10% to about 200%, even more preferably from about 20% to about 150%, and most preferably from about 25% to about 120% of the USRDI of such vitamin.

Non-limiting examples of such further vitamins and minerals, include niacin, thiamin, folic acid, pantothenic acid, biotin, vitamin A, vitamin C, vitamin B<sub>2</sub>, vitamin B<sub>3</sub>, vitamin B<sub>6</sub>, vitamin B<sub>12</sub>, vitamin D, vitamin E, vitamin K, iron, zinc, copper, phosphorous, iodine, chromium, molybdenum, and fluoride. Preferably, wherein a further vitamin or mineral is utilized the vitamin or mineral is selected from niacin, thiamin, folic acid, iodine, vitamin A, vitamin C, vitamin B<sub>6</sub>, vitamin B<sub>12</sub>, vitamin D, vitamin E, iron, zinc, and calcium. Preferably, at least one vitamin is selected from vitamin C, vitamin B<sub>6</sub>, vitamin B<sub>12</sub>, vitamin E, pantothenic acid, niacin, and biotin. Also preferably, the composition comprises vitamin C and one or more other vitamins selected from vitamin B<sub>6</sub>, vitamin B<sub>12</sub>, vitamin E, pantothenic acid, niacin, and biotin.

Commercially available vitamin A sources may also be included in the present compositions. As used herein, "vitamin A" includes, but is not limited to, vitamin A (retinol),  $\beta$ -carotene, retinol palmitate, and retinol acetate. The vitamin A may be in any form, for example, an oil, beadlets, or encapsulated. Wherein vitamin A is present in the compositions herein, the product comprises at least about 1%, preferably at least about 5%, more preferably from about 10% to about 200%, even more preferably from about 15% to about 150%, and most preferably from about 20% to about 120% of the USRDI of such vitamin. Wherein vitamin A is present in the compositions herein, it is especially preferred to include about 25% of the USRDI of vitamin A. The quantity of vitamin A to be added is dependent on processing conditions and the amount of

vitamin A deliver desired after storage. Preferably, wherein vitamin A is included within the present compositions, the compositions comprise from about 0.0001% to about 0.2%, more preferably from about 0.0002% to about 0.12%, also preferably from about 0.0003% to about 0.1%, even more preferably from about 0.0005% to about 0.08%, and most preferably from about 0.001% to about 0.06% of vitamin A, by weight of the product.

Commercially available sources of vitamin B<sub>2</sub> (also known as riboflavin) may be utilized in the present compositions. Wherein vitamin B<sub>2</sub> is present in the compositions herein, the product comprises at least about 1%, preferably at least about 5%, more preferably from about 5% to about 200%, even more preferably from about 10% to about 150%, and most preferably from about 10% to about 120% of the USRDI of such vitamin. Wherein vitamin B<sub>2</sub> is present in the compositions herein, it is especially preferred to include from about 15% to about 35% of the USRDI of vitamin B<sub>2</sub>.

Vitamin C (ascorbic acid) is a particularly preferred optional ingredient for use herein. Without intending to be limited by theory, it is believed that vitamin C may be utilized to enhance the benefits herein, by serving as a co-factor for the enzyme which cross-links collagen.

Encapsulated ascorbic acid and edible salts of ascorbic acid can also be used. Wherein vitamin C is present in the compositions herein, the product comprises at least about 1%, preferably at least about 5%, more preferably from about 10% to about 200%, even more preferably from about 20% to about 150%, and most preferably from about 25% to about 120% of the USRDI of such vitamin. Wherein vitamin C is present in the compositions herein, it is especially preferred to include about 100% of the USRDI of vitamin C. The quantity of vitamin C to be added is dependent on processing conditions and the amount of vitamin C deliver desired after storage. Preferably, wherein vitamin C is included within the present compositions, the compositions comprise from about 0.005% to about 0.2%, more preferably from about 0.01% to about 0.12%, also preferably from about 0.02% to about 0.1%, even more preferably from about 0.02% to about 0.08%, and most preferably from about 0.03% to about 0.06% of vitamin C, by weight of the product.

Nutritionally supplemental amounts of other vitamins which may be incorporated herein include, but are not limited to, vitamins B<sub>6</sub> and B<sub>12</sub>, folic acid, niacin, pantothenic acid, folic acid, vitamin D, and vitamin E. Wherein the product comprises one of these vitamins, the product preferably comprises at least 5%, preferably at least 25%, and most preferably at least 35% of the USRDI for such vitamin.

Minerals which may optionally be included in the compositions herein are, for example, calcium, manganese, magnesium, boron, zinc, iodine, iron, and copper. Minerals may be, for example, salts, chelated, complexed, or in colloidal form.

Any soluble salt of these minerals suitable for inclusion edible compositions can be used, for example, magnesium citrate, magnesium gluconate, magnesium sulfate, zinc chloride, zinc sulfate, potassium iodide, copper sulfate, copper gluconate, and copper citrate.

Manganese is a particularly preferred mineral for use herein, as this mineral is involved in the synthesis of glycosaminoglycans, collagen, and glycoproteins. Additionally manganese deficiencies can lead to abnormal bone growth, inflamed joints, bone loss, and arthritis. Manganese ascorbate is a particularly preferred form of manganese for use herein. Typical manganese dosages range from about 0 mg to about 1000 mg, more preferably from about 50 mg to about 950 mg, and most preferably from about 50 mg to about 250 mg for a human or large mammal (e.g., horse).

Boron is a particularly preferred mineral for use herein, as this mineral is necessary for osteocalcin formation in bone.

Calcium is a particularly preferred mineral for use in the present invention. Preferred sources of calcium include, for example, amino acid chelated calcium, calcium carbonate, calcium oxide, calcium hydroxide, calcium sulfate, calcium chloride, calcium phosphate, calcium hydrogen phosphate, calcium dihydrogen phosphate, calcium citrate, calcium malate, calcium titrate, calcium gluconate, calcium realate, calcium tartrate, and calcium lactate, and in particular calcium citrate-malate. The form of calcium citrate-malate is described in, e.g., Mehansho et al., U.S. Patent No. 5,670,344, issued September 23, 1997; Diehl et al., U.S. Patent No. 5,612,026, issued March 18, 1997; Andon et al., U.S. Patent No. 5,571,441, issued November 5, 1996; Meyer et al., U.S. Patent No. 5,474,793, issued December 12, 1995; Andon et al., U.S. Patent No. 5,468,506, issued November 21, 1995; Burkes et al., U.S. Patent No. 5,445,837, issued August 29, 1995; Dake et al., U.S. Patent No. 5,424,082, issued June 13, 1995; Burkes et al., U.S. Patent No. 5,422,128, issued June 6, 1995; Burkes et al., U.S. Patent No. 5,401,524, issued March 28, 1995; Zuniga et al., U.S. Patent No. 5,389,387, issued February 14, 1995; Jacobs, U.S. Patent No. 5,314,919, issued May 24, 1994; Saltman et al., U.S. Patent No. 5,232,709, issued August 3, 1993; Camden et al., U.S. Patent No. 5,225,221, issued July 6, 1993; Fox et al., U.S. Patent No. 5,215,769, issued June 1, 1993; Fox et al., U.S. Patent No. 5,186,965, issued February 16, 1993; Saltman et al., U.S. Patent No. 5,151,274, issued September 29, 1992; Kochanowski, U.S. Patent No. 5,128,374, issued July 7, 1992; Mehansho et al., U.S. Patent No. 5,118,513, issued June 2, 1992; Andon et al., U.S. Patent No. 5,108,761, issued April 28, 1992; Mehansho et al., U.S. Patent No. 4,994,283, issued February 19, 1991; Nakel et al., U.S. Patent No. 4,786,510, issued November 22, 1988; and Nakel et al., U.S. Patent No. 4,737,375, issued April 12, 1988. Preferred compositions of the present invention will comprise from about 0.01% to about 0.5%, more preferably from about 0.03% to about 0.2%, even more preferably from about 0.05% to about 0.15%, and most preferably from about 0.1% to about 0.15% of calcium, by weight of the product.

Iron may also be utilized in the compositions and methods of the present invention. Acceptable forms of iron are well-known in the art. The amount of iron compound incorporated into the product will vary widely depending upon the level of supplementation desired in the final product and the targeted consumer. Iron fortified compositions of the present invention typically contain from about 5% to about 100%, preferably from about 15% to about 50%, and most preferably about 20% to about 40% of the USRDI for iron.

Ferrous iron is typically better utilized by the body than ferric iron. Highly bioavailable ferrous salts that can be used in the ingestible compositions of the present invention are ferrous sulfate, ferrous fumarate, ferrous succinate, ferrous gluconate, ferrous lactate, ferrous tartarate, ferrous citrate, ferrous amino acid chelates, as well as mixtures of these ferrous salts. While ferrous iron is typically more bioavailable, certain ferric salts can also provide highly bioavailable sources of iron. Highly bioavailable ferric salts that can be used in the food or beverage compositions of the present invention are ferric saccharate, ferric ammonium citrate, ferric citrate, ferric sulfate, as well as mixtures of these ferric salts. Combinations or mixtures of highly bioavailable ferrous and ferric salts can be used in these edible mixes and ready-to-serve beverages. The preferred sources of highly bioavailable iron are ferrous fumarate and ferrous amino acid chelates.

Ferrous amino acid chelates particularly suitable as highly bioavailable iron sources for use in the present invention are those having a ligand to metal ratio of at least 2:1. For example, suitable ferrous amino acid chelates having a ligand to metal mole ratio of two are those of formula:



where L is an alpha amino acid, dipeptide, tripeptide, or quadrapeptide ligand. Thus, L can be any ligand which is a naturally occurring alpha amino acid selected from alanine, arginine, asparagine, aspartic acid, cysteine, cystine, glutamine, glutamic acid, glycine, histidine, hydroxyproline, isoleucine, leucine, lysine, methionine, ornithine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine; or dipeptides, tripeptides, or quadrapeptides formed by any combination of these alpha amino acids. See e.g., Ashmead et al., U.S. Patent No. 4,863,898, issued September 5, 1989; Ashmead, U.S. Patent No. 4,830,716, issued May 16, 1989; and Ashmead, U.S. Patent No. 4,599,152, issued July 8, 1986, all of which are incorporated by reference. Particularly preferred ferrous amino acid chelates are those where the reacting ligands are glycine, lysine, and leucine. Most preferred is the ferrous amino acid chelate sold under the mark Ferrochel® (Albion Laboratories, Salt Lake City, Utah) wherein the ligand is glycine.

In addition to these highly bioavailable ferrous and ferric salts, other sources of bioavailable iron can be included in the food and beverage compositions of the present invention. Other sources of iron particularly suitable for fortifying compositions of the present invention

included certain iron-sugar-carboxylate complexes. In these iron-sugar-carboxylate complexes, the carboxylate provides the counterion for the ferrous (preferred) or ferric iron. The overall synthesis of these iron-sugar-carboxylate complexes involves the formation of a calcium-sugar moiety in aqueous media (for example, by reacting calcium hydroxide with a sugar, reacting the iron source (such as ferrous ammonium sulfate) with the calcium-sugar moiety in aqueous media to provide an iron-sugar moiety, and neutralizing the reaction system with a carboxylic acid (the "carboxylate counterion") to provide the desired iron-sugar-carboxylate complex. Sugars that can be used to prepare the calcium-sugar moiety include any of the ingestible saccharidic materials, and mixtures thereof, such as glucose, sucrose and fructose, mannose, galactose, lactose, maltose, and the like, with sucrose and fructose being the more preferred. The carboxylic acid providing the "carboxylate counterion" can be any ingestible carboxylic acid such as citric acid, malic acid tartaric acid, lactic acid, succinic acid, propionic acid, etc., as well as mixtures of these acids.

These iron-sugar-carboxylate complexes can be prepared in the manner described in, e.g., Nakel et al., U.S. Patent Nos. 4,786,510 and 4,786,518, issued November 22, 1988, both of which are incorporated by reference. These materials are referred to as "complexes", but they may exist in solution as complicated, highly hydrated, protected colloids; the term "complex" is used for the purpose of simplicity.

Zinc may also be utilized in the compositions and methods of the present invention. Acceptable forms of zinc are well-known in the art. Zinc fortified compositions of the present invention typically contain from about 5% to about 100%, preferably from about 15% to about 50%, and most preferably about 25% to about 45% of the USRDI for zinc. The zinc compounds which can be used in the present invention can be in any of the commonly used forms such as, e.g., zinc sulfate, zinc chloride, zinc acetate, zinc gluconate, zinc ascorbate, zinc citrate, zinc aspartate, zinc picolinate, amino acid chelated zinc, and zinc oxide. Zinc gluconate and amino acid chelated zinc are particularly preferred.

#### Flavoring Agents

One or more flavoring agents are recommended for the embodiments of the present invention in order to enhance their palatability. Any natural or synthetic flavor agent can be used in the present invention. For example, one or more botanical and / or fruit flavors may be utilized herein. As used herein, such flavors may be synthetic or natural flavors.

Particularly preferred fruit flavors are exotic and lactonic flavors such as, for example, passion fruit flavors, mango flavors, pineapple flavors, cupuacu flavors, guava flavors, cocoa flavors, papaya flavors, peach flavors, and apricot flavors. Besides these flavors, a variety of other fruit flavors can be utilized such as, for example, apple flavors, citrus flavors, grape flavors, raspberry flavors, cranberry flavors, cherry flavors, grapefruit flavors, and the like. These fruit

flavors can be derived from natural sources such as fruit juices and flavor oils, or may alternatively be synthetically prepared.

Preferred botanical flavors include, for example, tea (preferably black and green tea, most preferably green tea), aloe vera, guarana, ginseng, ginkgo, hawthorn, hibiscus, rose hips, chamomile, peppermint, fennel, ginger, licorice, lotus seed, schizandra, saw palmetto, sarsaparilla, safflower, St. John's Wort, curcuma, cardimom, nutmeg, cassia bark, buchu, cinnamon, jasmine, haw, chrysanthemum, water chestnut, sugar cane, lychee, bamboo shoots, vanilla, coffee, and the like. Preferred among these is tea, guarana, ginseng, ginkgo, and coffee. In particular, the combination of tea flavors, preferably green tea or black tea flavors (preferably green tea), optionally together with fruit flavors has an appealing taste. In another preferred embodiment, coffee is included within the present compositions. A combination of green tea and coffee in the present compositions is often preferred.

The flavor agent can also comprise a blend of various flavors. If desired, the flavor in the flavoring agent may be formed into emulsion droplets which are then dispersed in the beverage composition or concentrate. Because these droplets usually have a specific gravity less than that of water and would therefore form a separate phase, weighting agents (which can also act as clouding agents) can be used to keep the emulsion droplets dispersed in the beverage composition or concentrate. Examples of such weighting agents are brominated vegetable oils (BVO) and resin esters, in particular the ester gums. See L.F. Green, Developments in Soft Drinks Technology, Vol. 1, Applied Science Publishers Ltd., pp. 87-93 (1978) for a further description of the use of weighting and clouding agents in liquid beverages. Typically the flavoring agents are conventionally available as concentrates or extracts or in the form of synthetically produced flavoring esters, alcohols, aldehydes, terpenes, sesquiterpenes, and the like.

#### Coloring Agent

Small amounts of one or more coloring agents may be utilized in the compositions of the present invention. FD&C dyes (e.g., yellow #5, blue #2, red # 40) and / or FD&C lakes are preferably used. By adding the lakes to the other powdered ingredients, all the particles, in particular the colored iron compound, are completely and uniformly colored and a uniformly colored beverage mix is attained. Preferred lake dyes which may be used in the present invention are the FDA-approved Lake, such as Lake red #40, yellow #6, blue #1, and the like. Additionally, a mixture of FD&C dyes or a FD&C lake dye in combination with other conventional food and food colorants may be used. Riboflavin and b-carotene may also be used. Additionally, other natural coloring agents may be utilized including, for example, fruit, vegetable, and / or plant extracts such as grape, black currant, aronia, carrot, beetroot, red cabbage, and hibiscus.

The amount of coloring agent used will vary, depending on the agents used and the intensity desired in the finished product. The amount can be readily determined by one skilled in

the art. Generally, if utilized, the coloring agent should be present at a level of from about 0.0001% to about 0.5%, preferably from about 0.001% to about 0.1%, and most preferably from about 0.004% to about 0.1%, by weight of the composition.

#### Preservatives

Optionally, one or more preservatives may additionally be utilized herein. Preferred preservatives include, for example, sorbate, benzoate, and polyphosphate preservatives.

Preferably, wherein a preservative is utilized herein, one or more sorbate or benzoate preservatives (or mixtures thereof) are utilized. Sorbate and benzoate preservatives suitable for use in the present invention include sorbic acid, benzoic acid, and salts thereof, including (but not limited to) calcium sorbate, sodium sorbate, potassium sorbate, calcium benzoate, sodium benzoate, potassium benzoate, and mixtures thereof. Sorbate preservatives are particularly preferred. Potassium sorbate is particularly preferred for use in the present invention.

Wherein a composition comprises a preservative, the preservative is preferably included at levels from about 0.0005% to about 0.5%, more preferably from about 0.001% to about 0.4% of the preservative, still more preferably from about 0.001% to about 0.1%, even more preferably from about 0.001% to about 0.05%, and most preferably from about 0.003% to about 0.03% of the preservative, by weight of the composition. Wherein the composition comprises a mixture of one or more preservatives, the total concentration of such preservatives is preferably maintained within these ranges.

#### Emulsifiers and Oils

One or more emulsifiers and / or oils may also be included in the present compositions for texture and opacity purposes. Typical emulsifiers and oils useful herein include, for example, mono-di glycerides, lecithin, pulp, cotton seed oil, and vegetable oil.

#### Carbonation Component

Carbon dioxide can be introduced into the water which is mixed with a beverage concentrate or into the beverage composition after dilution to achieve carbonation. The carbonated beverage can be placed into a container, such as a bottle or can, and then sealed. Any conventional carbonation methodology may be utilized to make carbonated beverage compositions of this invention. The amount of carbon dioxide introduced into the beverage will depend upon the particular flavor system utilized and the amount of carbonation desired.

#### The Information Used in the Present Kits and Methods

In one embodiment of the present invention, the kits further comprise information selected from the group consisting of:

- (i) dose-form information;
- (ii) instruction or suggestion of ingestion of the composition within about 4 hours of ingestion of a food or beverage; and

(iii) combinations thereof.

As the present inventors have discovered, this information is critical to the success of the compositions herein. For example, the present inventors have surprisingly discovered that the behavior of the consumer in need of treatment affects the success of the chondroprotective regimen. In particular, the relationship between 1) ingestion of a particular form of chondroprotective composition; and 2) food or beverage intake has been found to be critical to the success of the regimen. Accordingly, the information described herein, which guides the consumer toward an optimized regimen, is a critical and surprisingly effective element of the present invention.

Accordingly, the present kits comprise an aqueous chondroprotective composition as well as information which improves or aids efficacy of the composition. In particular, the kits comprise information which informs the consumer that aqueous chondroprotective compositions provide enhanced efficacy relative to dry-form chondroprotective compositions having the same, or similar, chondroprotective agent. Alternatively or additionally, the kits comprise information which instructs or suggests ingestion of the composition within about 4 hours of ingestion of a food or beverage. As the ordinarily skilled artisan will understand, the information defined within the present invention is not limited to specific words or descriptions herein.

As is well-known, language used to provide information can be modified extensively without substantially modifying the overall message to the consumer. Accordingly, the descriptions which follow are not intended to be limiting in any way, but serve to exemplify the particular information which is important for the success of the present regimens.

The information included within the kit may be in the form of words, pictures, symbols, and / or the like. The information may, as non-limiting examples, be present on: 1) a label visible on the exterior of packaging (e.g., a label on a bottle, carrier, or case); or 2) a packaging insert included within the packaging utilized (including, for example, within carriers, cases, or even under a bottle cap). Additionally, the information of the kit need not be physically present with the aqueous chondroprotective composition. For example, the information may be associated with the composition, for example, advertising or information accessible by computer (e.g., the internet), television, print advertisement, and physician recommendations).

In a particularly preferred embodiment, the information is printed on a device containing the composition, e.g., a bottle. These preferred kits may be in the form of one bottle containing the composition, or may be obtained as a plurality of bottles each containing the composition. For example, the kits may be obtained as one bottle, or cases of four, six, seven (e.g., a weekly supply), or eight bottles co-packaged together. Additionally, monthly kits may be obtained as cases of, for example, twenty-eight or thirty bottles co-packaged together.

The information need not use the actual words described herein (e.g., "enhanced efficacy"). The information is preferably presented in a manner such that the consumer can



readily understand and follow the instructions. Preferably, the information is provided at a low readability level, i.e., is written such that the average consumer can understand the information. Complex and difficult medical terminology or diagnostic indicators (e.g., photos showing a clinical difference between subjects treated with traditional products and subjects treated with the compositions herein) are preferably translated into more simple words, pictures, and / or symbols. The readability level of the information is very important since it has been reported that patients do not understand many medical terms used in typical patient information materials. See e.g., D.L. Smith, "Compliance Packaging: A Patient Education Tool", *Amer. Pharm.*, Vol. NS29, No. 2, p. 42 - 53 (1989).

A. Dose-form Information

As stated, the present inventors have discovered that efficacy of chondroprotective compositions is unexpectedly related to the particular form of chondroprotective composition used. In particular, the present inventors have discovered that the aqueous chondroprotective compositions used herein provide substantially increased efficacy, and thus health benefit, relative to the corresponding dry-forms. As used herein, the "corresponding dry-form" will contain the same chondroprotective agent(s) as the aqueous chondroprotective composition to which it is compared. However, this "corresponding dry-form" comprises less than about 2% water, by weight of the dry-form composition.

Dry-form compositions comprise less than about 2% water, by weight of the composition. Preferably, dry-form compositions comprise less than about 1% water, by weight of the composition. Most preferably, dry-form compositions comprise less than about 0.5% water, by weight of the composition.

Non-limiting examples of dry-form compositions include tablets, capsules, pills, granules, and powders. Dry-form compositions are often compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Dry-form compositions will often contain one or more conventional adjuvants such as inert diluents, for example, calcium carbonate, sodium carbonate, mannitol, lactose and cellulose; binders such as starch, gelatin and sucrose; disintegrants such as starch, alginic acid and croscarmellose; lubricants such as magnesium stearate, stearic acid, and talc. Glidants such as silicon dioxide can be used to improve flow characteristics of the powder mixture. Coloring agents, such as the FD&C dyes are often added for appearance. Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors, are useful adjuvants for chewable tablets.

As used herein, the "dose-form information" distinguishes efficacy of the present aqueous chondroprotective compositions from that exhibited by the foregoing dry-form compositions. Such information will inform the consumer (by words, pictures, symbols and / or the like) that use of the

aqueous chondroprotective present as part of the kit will exhibit enhanced efficacy relative to a dry-form composition, for example, a corresponding dry-form composition.

It is therefore necessary to inform the consumer that use of the present aqueous chondroprotective compositions will provide an enhanced health benefit (e.g., a joint health benefit, bone health benefit, cardiac health benefit, and / or anti-inflammation benefit) relative to dry-form compositions). Preferably, the dose-form information will inform the consumer that the present aqueous chondroprotective compositions provide an enhanced joint health benefit, bone health benefit, and / or anti-inflammation benefit relative to the dry-form composition. It is most preferred to convey that a joint health benefit is optimized through use of the present aqueous chondroprotective compositions, relative to the dry-form composition.

Non-limiting examples of such dose-form information include the following phrases (other words, pictures, symbols, and / or the like can alternatively be used to convey the same or similar meaning):

1. "More efficacious than tablets or capsules."
2. "More efficacious than X-Brand Joint Improver" (i.e., any brand name of dry-form chondroprotective product).
3. "Works better than tablets, capsules, pills, or powders."
4. "Scientists have found that this product works better than the leading tablets, capsules, pills, and powders."
5. "Clinically-proven to provide better joint flexibility than the leading tablet."
6. "Clinically-proven to decrease the pain associated with inflammation – even better than the leading tablet!"
7. "Helps restore your joint and bone health in a way that no tablet or capsule can."
8. "Each day of treatment helps your joints better than the leading tablet."
9. "Just think – freedom from your symptoms is now nearer than when you took the leading tablet!"
10. "You are now in control of you symptoms – you have just purchased the best available joint health product on the market."
11. "You can feel relief faster because this product is more efficacious and more bioavailable than tablets."

B. Instruction or Suggestion of Ingestion Within About 4 Hours of Ingestion of a Food or Beverage

As stated, the present inventors have discovered that efficacy of the chondroprotective composition is also enhanced wherein the composition is ingested within about 4 hours of ingestion of a food or beverage, relative to not consuming a food or beverage during this time period. In addition to this finding, it has been surprisingly discovered that the efficacy of aqueous chondroprotective compositions is significantly greater relative to that of dry forms of

chondroprotective compositions (e.g., tablets or capsules), even wherein each of these compositions is ingested within about 4 hours of ingestion of a food or beverage.

It has therefore been discovered that efficacy of the chondroprotective regimen is dependent upon food or beverage intake and, in order to provide efficacious treatments, consumers need to be aware of this discovery. Accordingly, the present kits further comprise information which is instruction or suggestion of ingestion of the chondroprotective composition within about 4 hours of ingestion of a food or beverage. As used herein, "instruction of ingestion of the composition" is information which instructs the consumer to ingest the composition within about 4 hours of ingestion of a food or beverage. As used herein, "suggestion of ingestion of the composition" is information which merely suggests this use or merely informs the consumer that certain results may be achieved when ingested within about 4 hours of ingestion of a food or beverage.

As also used herein, the term "ingested within about 4 hours of ingestion of a food or beverage" includes within both about 4 hours before or after ingestion of a chondroprotective composition described herein. Additionally, "within about 4 hours" includes any amount of time which is less than, or equal to, about 4 hours. For example, "within about 4 hours" includes within about 3 hours, within about 2 hours, within about 1 hour, within about 45 minutes, and even concurrently with ingestion of a food or beverage. As used herein, "concurrently" means ingestion of a chondroprotective composition as described herein at about the same time as ingesting a food or beverage, within about fifteen to about thirty minutes after completely ingesting a food or beverage, or within about fifteen to about thirty minutes before commencing the ingestion of a food or beverage. As further used herein, the term "concurrently" includes instruction to ingest the chondroprotective composition "with a food or beverage." Preferably, the food or beverage is ingested within about 2 hours, more preferably within about 1 hour, and most preferably concurrently with, ingestion of the chondroprotective composition.

The chondroprotective composition may be in any form, e.g., a ready-to-drink beverage composition or a concentrate which is formulated by the consumer. Therefore, "within about 4 hours of ingestion of a food or beverage" refers to a food or beverage which is additional to the chondroprotective composition ingested herein. The food or beverage ingested is not limited and need not be specifically described in the information (i.e., the information may be "for best results, take this product with the food of your choice"). Most preferably, the present kits comprise information that the aqueous chondroprotective composition should be ingested within about 4 hours of ingestion of a food. Such food may be a full meal (e.g., a meal comprised of a meat and vegetable) or a snack (e.g., a piece of fruit, crackers, or a candy bar). Therefore, the information may instruct or suggest ingestion of a chondroprotective composition within 4 hours of ingestion of breakfast, lunch, dinner, or a snack.

The food or beverage preferably comprises at least one of a carbohydrate, fat, or protein source. Non-limiting examples of foods include fruits, vegetables, savory snacks (e.g., potato chips and pretzels), cracker snacks (e.g., cheese and cracker snacks), health bars (e.g., PowerBar® (commercially available from PowerBar Inc., Berkeley, CA), NutriGrain® Bar (commercially available from Kellogg's), HeartBar (commercially available from Cooke Pharma, Belmont, CA), and Clif Bar® and Luna Bar® (both commercially available from Clif Bar, Inc., Berkeley, CA), and Prevesse®, commercially available from Procter & Gamble Co., Cincinnati, OH)), yogurts, cheeses, breads, cereals, meat products, rice products, and baked goods (e.g., cookies and other snack foods). Most preferably, the food is a health bar. Non-limiting examples of beverages include fruit juices (including all levels of fruit juice), milk products, sodas, and coffee products.

Preferably, the food or beverage is nutritionally-balanced. As used herein, the term "nutritionally-balanced", means that that a single serving or reference serving of the food provides a nutritionally desirable level of fat, protein or amino acid source, and dietary fiber. Preferably, "nutritionally balanced" foods provide a relatively low level of digestible fat (e.g., about 3 grams or less per reference serving and / or about 27% or less of total calories from fat), are a good source of dietary protein or other amino acid source (e.g., about 5 g or more per reference serving and / or about 19% or more of total calories from protein), and / or are a good source of dietary fiber (e.g., about 2.5 g or more of dietary fiber per reference serving). More preferably, "nutritionally balanced" foods provide a relatively low level of digestible fat (e.g., about 3 grams or less per reference serving and / or about 27% or less of total calories from fat), are a good source of dietary protein or other amino acid source (e.g., about 5 g or more per reference serving and about 19% or more of total calories from protein), and / or are a good source of dietary fiber (e.g., about 2.5 g or more of dietary fiber per reference serving).

Preferably, the kit is labeled with the time of day that the chondroprotective composition is to be administered, for example, "Breakfast", "Lunch", "Dinner" and / or "Snack" (i.e., between, before, and / or after a meal). This aids the consumer to ingest the aqueous chondroprotective composition with a meal or snack. It is a preferred embodiment of the present invention to inform or suggest the consumer to ingest the chondroprotective composition within 4 hours of ingestion of breakfast or dinner, preferably breakfast.

Since ingestion of a food or beverage is important, the information of the kit may also be, for example, recipes and healthy diet literature which recommends the ingestion of healthy foods to the user.

Preferably, the information will inform the consumer that the present aqueous chondroprotective compositions provide an enhanced joint health benefit, bone health benefit, and / or anti-inflammation when ingested within about 4 hours of ingestion of a food or beverage.

It is most preferred to convey that a joint health, bone health, and / or anti-inflammation benefit is enhanced. Most preferably, the Information conveys that a joint health benefit is enhanced.

Non-limiting examples of such information include the following phrases (other words, pictures, symbols, and / or the like can alternatively be used to convey the same or similar meaning):

1. "For best results, take this product with food or soft drink."
2. "For best results, take this product with your favorite meal."
3. "We suggest taking this product around the time of a meal or snack."
4. "For best results, take this product with a healthy diet."
5. "For best results, take this product with your favorite healthy meal - full of proteins and carbohydrates."
6. "Drink this product with breakfast for optimal performance."
7. "A healthy lifestyle includes eating the right meal before or after you drink this product."
8. "Your flexibility performance will be optimal if you take this product around the time you eat your favorite snack or meal."
9. "Your joints will appreciate a snack with this product!"

#### The Separate Food or Beverage of the Present Kits

In yet another embodiment of the present invention, the kits comprise:

- (a) a composition comprising one or more chondroprotective agents and at least about 80% water; and
- (b) a separate food or beverage.

As has been stated, the present inventors have discovered that efficacy of the chondroprotective composition is enhanced wherein the composition is ingested within about 4 hours of a food or beverage, relative to not consuming a food or beverage during this time period. Therefore, as has been discovered, in order to provide an efficacious chondroprotective regimen, it is important for the consumer to have access not only to the composition comprising the chondroprotective agent, but also a separate food or beverage. This ensures compliance with the optimal regimen described herein, particularly for the modern consumer who is extremely busy with the tasks and responsibilities of daily life. It is understood herein that the composition comprising the chondroprotective agent and water may, and often will be, a beverage composition. Thus, the "separate food or beverage" is a distinct composition which may be, for example, a solid or semi-solid food, or even a further beverage composition. Preferably, the kit comprises a separate food. As will be understood herein, the importance is that a source of one or more of a carbohydrate, fat (lipid), protein, or other common food component is included as a

composition which is separate from the chondroprotective composition also provided within the kit.

As stated, the separate food or beverage preferably comprises at least one of a carbohydrate, fat, or protein source. Non-limiting examples of separate foods include fruits, vegetables, savory snacks (e.g., potato chips and pretzels), cracker snacks (e.g., cheese and cracker snacks), health bars (e.g., PowerBar® (commercially available from PowerBar Inc., Berkeley, CA), NutriGrain® Bar (commercially available from Kellogg's), HeartBar (commercially available from Cooke Pharma, Belmont, CA), and Clif Bar® and Luna Bar® (both commercially available from Clif Bar, Inc., Berkeley, CA), and Prevesse®, commercially available from Procter & Gamble Co., Cincinnati, OH)), yogurts, cheeses, breads, cereals, meat products, rice products, and baked goods (e.g., cookies and other snack foods). Most preferably, the separate food is a health bar. Non-limiting examples of separate beverages include fruit juices (including all levels of fruit juice), milk products, sodas, and coffee products.

Preferably, the separate food or beverage is nutritionally-balanced. As used herein, the term "nutritionally-balanced", means that that a single serving or reference serving of the food provides a nutritionally desirable level of fat, protein or amino acid source, and dietary fiber. Preferably, "nutritionally balanced" foods provide a relatively low level of digestible fat (e.g., about 3 grams or less per reference serving and / or about 27% or less of total calories from fat), are a good source of dietary protein or other amino acid source (e.g., about 5 g or more per reference serving and / or about 19% or more of total calories from protein), and / or are a good source of dietary fiber (e.g., about 2.5 g or more of dietary fiber per reference serving). More preferably, "nutritionally balanced" foods provide a relatively low level of digestible fat (e.g., about 3 grams or less per reference serving and / or about 27% or less of total calories from fat), are a good source of dietary protein or other amino acid source (e.g., about 5 g or more per reference serving and about 19% or more of total calories from protein), and / or are a good source of dietary fiber (e.g., about 2.5 g or more of dietary fiber per reference serving).

The kits comprising the separate food or beverage may optionally further comprise:

- (a) the foregoing dose-form information;
- (b) the foregoing instruction or suggestion of ingestion of the composition within about 4 hours of ingestion of the separate food or beverage; or
- (c) combinations thereof.

#### Methods of the Present Invention

The methods of the present invention comprise enhancing a benefit associated with a composition comprising one or more chondroprotective agents and water, the method comprising orally administering to a mammal the composition within about 4 hours of oral administration of a food or beverage.

The compositions are preferably administered to mammals who experience joint and / or bone dysfunction or those who desire to maintain current joint and / or bone function (*i.e.*, prophylactic use). The compositions of this invention may be ingested as a supplement to normal dietetic requirements. Frequency of administration is not limited, however, such administration is typically at least once weekly, more preferably at least 3 times weekly, and most preferably at least once daily.

As used herein, the term "orally administering" with respect to the mammal (preferably, human) means that the mammal ingests or is directed to ingest (preferably, for the purpose of providing joint and / or bone health): 1) one or more aqueous chondroprotective compositions of the present invention; and also according to the method 2) a food or beverage within 4 hours of administration of the composition. Preferably, the composition is a beverage composition having the foregoing preferred limitations. Preferably, the food or beverage is a food, having the foregoing preferred limitations. As set forth above, preferably the composition is administered within about 2 hours, more preferably within about 1 hour, and most preferably concurrently with administration of a food or beverage.

Wherein the mammal is directed to ingest one or more of the compositions or the food or beverage, such direction may be that which instructs and / or informs the user that use of the composition may and / or will provide one or more general health and / or general physiological benefits including, but not limited to, joint health, bone health, cardiac health, anti-inflammation, refreshment, satiation, and nutrition. Non-limiting examples of such instruction or information is set forth herein above as part of the description of the present kits.

For example, such direction may be oral direction (*e.g.*, through oral instruction from, for example, a physician, health professional, sales professional or organization, and / or radio or television media (*i.e.*, advertisement) or written direction (*e.g.*, through written direction from, for example, a physician or other health professional (*e.g.*, scripts), sales professional or organization (*e.g.*, through, for example, marketing brochures, pamphlets, or other instructive paraphernalia), written media (*e.g.*, internet, electronic mail, or other computer-related media), and / or packaging associated with the composition (*e.g.*, a label present on a package containing the composition). As used herein, "written" means through words, pictures, symbols, and / or other visible descriptors. Such direction need not utilize the actual words used herein, for example, "joint", "bone", "human", or "mammal", but rather use of words, pictures, symbols, and the like conveying the same or similar meaning are contemplated within the scope of this invention.

#### Methods of Making

The presently described aqueous chondroprotective compositions are made according to methods which will be well known by the ordinarily skilled artisan. To illustrate, the compositions

herein may be prepared by dissolving, dispersing, or otherwise mixing all components singularly or in suitable combinations together and in water where appropriate, agitating with a mechanical stirrer until all of the ingredients have been solubilized or adequately dispersed. Where appropriate, all separate solutions and dispersed may then be combined. When using the present chondroprotective agents which have been discovered to be pH sensitive as described herein, it may be important to adjust the desired pH with an acidulant and / or buffer system before adding the chondroprotective agent to the mixture. Wherein a shelf stable composition is desired, the final mixture can optionally, but preferably, be pasteurized or filled aseptically at appropriate process conditions.

In making a beverage composition, a beverage concentrate may optionally be formed first. One method to prepare the concentrate form of the beverage composition would be to start with less than the required volume of water that is used in the preparation of the beverage composition. Another method would be to partially dehydrate the finally prepared beverage compositions to remove only a portion of the water and any other volatile liquids present. Dehydration may be accomplished in accordance with well known procedures, such as evaporation under vacuum. The concentrate can be in the form of a relatively thick liquid. A syrup is typically formed by adding suitable ingredients such as electrolytes or emulsions to the beverage concentrate. The syrup is then mixed with water to form a finished beverage or finished beverage concentrate. The weight ratio of water to syrup is typically from about 1:1 to about 5:1.

Carbon dioxide can be introduced either into the water to be mixed with the beverage concentrate, or into the ready-to-drink beverage composition, to achieve carbonation. The carbonated beverage composition can then be stored in a suitable container and then sealed. Techniques for making and carbonating beverage embodiments of the present invention are described in the following references: L.F. Green (ed.), *Developments in Soft Drinks Technology*, Vol. 1 (Elsevier, 1978); G.S. Cattell and P.M. Davies, "Preparation and Processing of Fruit Juices, Cordials and Drinks", *Journal of the Society of Dairy Technology*, Vol. 38 (1), pp. 21-27, A.H. Varnam and J.P. Sutherland, *Beverages - Technology, Chemistry and Microbiology*, Chapman Hall, 1994; and A.J. Mitchell (ed.), *Formulation and Production of Carbonated Soft Drinks*, Blackie and Sons Ltd., 1990.

#### EXAMPLES

The following are non-limiting examples of the present kits and methods. The compositions utilized are prepared utilizing conventional methods. The following examples are provided to illustrate the invention and are not intended to limit the scope thereof in any manner.

##### Example 1



An 8 oz. ready-to-drink beverage composition is prepared by combining the following components in a conventional manner:

Component	Wt%
Glucosamine Hydrochloride	0.8
Fructose	9.3
Thickeners	0.04
Calcium citrate malate	0.67
Fruit Juice Concentrate	1.65
Natural Flavors	0.02
Ascorbic Acid	0.04
Citric Acid	0.35
Water	<i>quantum satis</i>

In a particularly preferred example of this beverage composition, approximately 1800 mg of the glucosamine hydrochloride is used in the composition. If needed, the pH of the beverage composition is adjusted to around 3.7. Various flavors of the beverage composition may be formulated according to standard techniques, for example, grapefruit and / or cranberry flavors.

This composition is contained within a bottle. The bottle is labeled with various information, including the information described herein. The label states that "Best results are achieved when taking this product with food." The label also states that "This product provides greater joint health benefit relative to any benefit provided by the leading tablet or capsule."

As a result of the labeled information, a 45-year-old human female orally ingests the composition concurrently with her daily breakfast, which typically includes buttered toast and a banana. After ingesting the composition once-daily for about 4 weeks, she reports enhanced flexibility relative to when she was ingesting corresponding dry-forms.

#### Example 2

A 4 oz. ready-to-drink beverage composition is prepared by combining the following components in a conventional manner:

Component	Wt%
Glucosamine Hydrochloride	1.6
Fructose	9.3
Thickeners	0.04

Calcium citrate malate	1.14
Fruit Juice Concentrate	1.65
Natural Flavors	0.02
Ascorbic Acid	0.08
Citric Acid	0.35
Water	<i>quantum satis</i>

If needed, the pH of the beverage composition is adjusted to from about 3.7 to about 3.9. Various flavors of the beverage composition may be formulated according to standard techniques, for example, grapefruit and / or cranberry flavors. If desired, this beverage composition may be further diluted by the consumer prior to ingestion with additional water, or a beverage of the consumer's choice.

This composition is contained within a bottle. The bottle is labeled with various information, including the information described herein. The label instructs the consumer to "Take this product within about 1 hour of eating your favorite snack or meal." The label also instructs the consumer to "Take this product as a superior substitute to the leading capsule or tablet."

As a result of the labeled information, a 50-year-old human male orally ingests the composition. After ingesting the composition once-daily for about 4 weeks concurrently with his daily dinner, which typically includes meat and vegetables (e.g., a salad), he reports decreased joint pain relative to when he was ingesting corresponding dry-forms.

Example 3

A 2 oz. ready-to-drink beverage composition is prepared by combining the following components in a conventional manner:

Component	Wt%
Glucosamine Hydrochloride	3.2
Fructose	9.3
Thickeners	0.04
Calcium citrate malate	2.3
Natural Flavors	0.02
Ascorbic Acid	0.16
Citric Acid	0.35
Water	<i>quantum satis</i>

If needed, the pH of the beverage composition is adjusted to from about 3.7 to about 3.9. Various flavors of the beverage composition may be formulated according to standard techniques, for example, grapefruit and / or cranberry flavors. If desired, this beverage composition may be further diluted by the consumer prior to ingestion with additional water, or a beverage of the consumer's choice.

This composition is contained within a bottle. The bottle is labeled with various information, including the information described herein. The label instructs the consumer to "Add this to the water you provide with your pet's daily meal." The label also instructs the consumer to "Feed this as a substitute to the leading dry powder."

As a result of the labeled information, the owner of a large dog administers the composition to the dog. After the dog ingests the composition once-daily with his daily meal for about 4 weeks, the owner reports that the dog exhibits increased physical activity (including running and jumping) relative to when the dog was ingesting corresponding dry-forms.

Example 4

A kit according to the present invention comprises the composition according to Example 1 and a distinct, nutritionally-balanced health bar composition (having a filling (according to the

"filling formula") sandwiched between two "crackers" (according to the crumb formula) and having the following composition:

Ingredient	Crumb Formula grams/100 grams	Filling Formula grams/100 grams
62DE Corn Syrup (Quality Ingredients Corp., Chester, N.J.)	.061	
Olean® (Procter & Gamble Co., Cincinnati, OH.)	8.95	22.2
Malt Syrup (Hawkeye 5900 Quality Ingredients Corp., Chester N.J.)	1.22	
Natural Butter Flavor (Flavors of North America, Inc., Carol Stream, IL.)	1.47	
Processed De-fatted (20%) Peanut Flour from US#1 Medium Runner Peanuts (Cargill Peanut, Dawson GA.)		49.8
Sugar 12X (Amalgamated Sugar Co., Ogden, UT.)		13.8
Granulated Sugar (Holly Sugar Co., Worland, WY.)	5.49	
Salt - TFC Purex (Morton International, Inc., Philadelphia, PA.)	0.29	
Iodized Salt (Morton International, Inc., Chicago, IL.)		1.1
L-Cysteine HCl Monohydrate (Quality Ingredients Corp., Chester N.J.)	.041	
Lecithin - Centrophase HR (Central Soya Co., Inc., Fort Wayne, IN.)		.2
Flour - soft wheat (Siemer Milling Co., Teutopolis, IL.)	40.28	
Fiber - insoluble wheat (Vitacel® WF-600/30, J. Rettenmaier, Ellwangen/J, Germany)	2.94	
Fiberaid® (Larex Corp., White Bear Lake, MN.)	1.47	9.0
Isolated Soy Protein (Supro® 661, Protein Technologies Intl., St. Louis, MO.)	6.27	3.5
Sodium Bicarbonate (Church & Dwight Co.,	0.74	

Princeton, NJ.)		
Calcium Phosphate Monobasic (Regent 12XX, Rhodia, Cranbury, N.J.)	0.59	
Sodium Aluminum Phosphate (Levair, Rhodia, Cranbury, N.J.)	0.59	
Ammonium Bicarbonate (Church & Dwight Co., Princeton, NJ.)	1.86	
Whey Protein Isolate (BiPRO, Davisco Food International, Inc., Le Sueur, MN.)	2.69	
Water	19.40	
Wheat Gluten (Gluvtal 21000, Cerestar, Hammond, IN.)	1.96	
Calcium Carbonate (USP AlbaGlos, Specialty Minerals, Inc., Bethlehem, PA.)	1.96	
Egg White Solids (Henningsen Foods, Omaha, NE.)	0.98	
Constant Behenic Stabilizer (ADM, Macon, GA.)		0.4
Vitamin Mix: Components & ratios as listed below		0.8
Vitamin A,D3, K1 blend (Watson Foods Co., West Haven, CT.)		39.09
Vit E alpha-tocopherol acetate 50% type CWS/F (Roche Vitamins, Parsippany, NJ.)		19.81
(vit B1) Thiamine Hydrochloride (Roche Vitamins, Parsippany, NJ.)		0.75
(vit B2) Riboflavin (Roche Vitamins, Parsippany, NJ.)		0.82
(vit B3) Niacin USP FCC (Roche Vitamins, Parsippany, NJ.)		7.19
(vit B6) Pyridoxine Hydrochloride (Roche Vitamins, Parsippany, NJ.)		0.96
(vit B12) 1% Trituration of Vitamin B12 (Roche Vitamins, Parsippany, NJ.)		0.25
Vitamin C ultra fine powder (Roche Vitamins, Parsippany, NJ.)		21.55

Zinc Citrate Trihydrate (Tate & Lyle, Decatur, IL.)		6.88
Iron (reduced) (100% ) (Roche Vitamins, Parsippany, NJ.)		2.64

The health bar is manufactured under standard conditions well-known to one of ordinary skill in the art.

As stated in Example 1, the chondroprotective composition is contained within a bottle. The bottle is labeled with various information, including the information described herein. The label states that "Best results are achieved when taking this product with food." The label also states that "This product provides greater joint health benefit relative to any benefit provided by the leading tablet or capsule."

The health bar is packaged in a standard plastic wrapper, the chondroprotective composition is contained within a bottle, and the two of these are co-packaged (e.g., inside a containing device such as a box) as the kit. A 30-year-old athletic male obtains the kit, eats the health bar, and drinks the chondroprotective composition over a 15 minute period.

## WHAT IS CLAIMED IS:

1. A kit characterized by:
  - (a) a composition comprising one or more chondroprotective agents and at least about 80% water; and
  - (b) information selected from the group consisting of:
    - (i) dose-form information;
    - (ii) instruction or suggestion of ingestion of the composition within about 4 hours of ingestion of a food or beverage; and
    - (iii) combinations thereof.
2. A kit according to Claim 1 wherein the chondroprotective agent is selected from the group consisting of gelatin, cartilage, aminosugars, glycosaminoglycans, methylsulfonylmethane, precursors of methylsulfonylmethane, S-adenosylmethionine, salts thereof, and mixtures thereof.
3. A kit according to any of the preceding claims wherein the chondroprotective agent is selected from the group consisting of aminosugars and glycosaminoglycans.
4. A kit according to any of the preceding claims characterized by dose-form information.
5. A kit according to any of the preceding claims characterized by information which instructs or suggests ingestion of the composition within about 2 hours of ingestion of a food or beverage.
6. A kit according to any of the preceding claims wherein the chondroprotective agent is selected from the group consisting of glucosamine sulfate and glucosamine hydrochloride.
7. A kit according to any of the preceding claims characterized by information which instructs or suggests ingestion of the composition concurrently with ingestion of a food or beverage.
8. A kit according to any of the preceding claims wherein the composition further comprises one or more beverage components selected from the group consisting of fruit juice, tea solids, milk solids, fruit flavors, botanical flavors, and mixtures thereof.

9. A kit according to any of the preceding claims wherein the information is a package insert or is printed on a label affixed to a device containing the composition.
10. A kit characterized by:
  - (a) a composition comprising one or more chondroprotective agents and at least about 80% water; and
  - (b) a separate food or beverage.